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(12) (19) (CA) **Demande-Application**

(21) (A1) **2,287,501**
(86) 1998/04/20
(87) 1998/10/29

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(51) Int.Cl.[6] A61K 31/19, A61K 31/70
(30) 1997/04/21 (197 16 713.6) DE

(54) **THIOESTERS D'IBUPROFENE UTILISES COMME INHIBITEURS DE LA FORMATION DE MEDIATEURS D'INFLAMMATION ET DE DOULEUR NF-KB-DEPENDANTE**

(54) **IBUPROFEN THIOESTERS AS INHIBITORS OF NF-KB-DEPENDENT PAIN AND INFLAMMATION MEDIATOR FORMATION**

(57) L'invention concerne des médicaments contenant des CoA-thioesters d'acides arylpropioniques, d'acides arylacétiques ou acétylsalicylates, du R-ibuprofène ou des racémates d'ibuprofène, comportant jusqu'à 49 % de S-ibuprofène ou des dérivés des composés précités, qui sont métabolisés dans l'organisme de manière similaire. Selon l'invention, ces médicaments s'utilisent pour les indications de douleurs et d'inflammations aiguës et/ou chroniques, de toute origine, ainsi que pour lutter contre tous les autres symptômes de processus inflammatoires.

(57) The invention relates to medicaments containing Co-A thioesters of arylpropionic acids, arylacetic acids or acetylsalicylates, R-ibuprofen or ibuprofen racemates with up to 49 % S-ibuprofen or derivatives of the above-mentioned compounds, which are metabolized in an analog manner in the organism. According to the invention, said medicaments are used to indicate acute and/or chronic pain and all types of inflammations and to treat all other symptoms of inflammatory processes.

Abstract

Pharmaceutical preparations containing CoA-thioesters of arylpropionic acids, arylacetic acids or acetylsalicylates, R-ibuprofen or racemates of ibuprofen containing up to 49 % S-ibuprofen or derivatives of the said compounds which are metabolized in an analogous manner in the organism, are used according to the invention for the indications of acute or/and chronic pain, inflammation of any genesis and to treat any other symptoms of inflammatory processes.

Description

Ibuprofen thioesters as inhibitors of the Nf-κB-dependent formation of mediators of inflammation and pain.

(CoA-thioesters of arylpropionic acids, arylacetic acids and salicylates as inhibitors of the Nf-κB-dependent formation of mediators of inflammation and pain.)

The present invention concerns drugs which specifically and selectively block the activation of the transcription factor Nf-κB by inflammatory stimuli and thus selectively interfere with the development of symptoms of inflammation and pain.

Analgesics and anti-rheumatism agents are world-wide the most frequently used drugs. They are essentially composed of substances which inhibit the enzymes cyclo-oxygenase 1 and 2 (PGHS-1 and PGHS-2) (Frölich, TIBS, January 1997, (vol. 18), p. 30). This suppresses the formation of certain inflammatory mediators, the prostaglandins, and blocks the formation and perpetuation of inflammatory symptoms such as redness, swelling, warming, pain and reduced function (Vane and Botting (1996) overview - mechanism of action of anti-inflammatory drugs. In: Improved non-steroidal anti-inflammatory drugs - COX-2 enzyme inhibitors. ed.: Vane J.R., Botting J., Botting R., p. 1-27, Lancester: Kluwer Academic Publishers). In this connection it does not make any difference whether the inflammation that develops is due to injury (trauma), infections (bacteria, viruses, fungi), tumours or immunological

reactions (allergic reactions, autoimmune diseases). Recently an additional more specific therapeutic approach has been tried. The aim is to interrupt the activation process triggered by inflammatory stimuli such as phorbol esters or cytokines in the inflamed tissue leading to the formation of different inflammatory mediators by inhibiting the central transcription factor Nf-κB (Bauerle and Henkel, Annu. Rev. Immunol. (1994) 12, p. 141-179; Barnes and Adcock, TiPS, February 1997 (vol. 18), p. 46).

The previously used inhibitors of prostaglandin production, such as racemic ibuprofen, all have undesired pharmacological effects some of which are based on the inhibition of prostaglandin production by cyclooxygenase 1. Some organ systems such as the gastro-intestinal mucosa, renal tissue, pulmonary tissue and blood cells require the continuous production of prostaglandins by cyclooxygenase 1 which is present constitutively. Hence, when this enzyme system is inhibited, damage occurs (Vane and Botting, supra). Therefore the object of the present invention was to find substances which only or mainly prevent prostaglandin synthesis in connection with inflammatory processes, i.e. especially in the inflamed tissue, but do not affect production in all other tissues or only to a slight extent. Such drugs should be formed or activated for example only or mainly in the cells that are crucial for the inflammatory symptoms and only inhibit the cyclooxygenase 2 which is formed in these cells when inflammation occurs and additionally inhibit the formation of other inflammatory mediators.

This object is achieved according to the invention by a pharmaceutical preparation containing coA-thioesters of

arylpropionic acids, arylacetic acids or acetylsalicylates, R-ibuprofen or racemates of ibuprofen containing up to 49 % S-ibuprofen or derivatives of the said compounds which are metabolized in an analogous manner in the organism.

When analyzing the enantiomers of arylpropionic acids, i.e. known anti-inflammatory drugs, it turned out that the R-enantiomer of ibuprofen which was regarded as inactive (Evans, Eur. J. Clin. Pharmacol. (1992), 42, 237-256; Klein, "Therapiewoche Österreich", 8. December 1993, 12th ed. 652-657) is metabolized in the intermediary metabolism to R- and S-CoA thioesters (Menzel et. al. Biochemical Pharmacology (1994), vol. 48, No. 5, p. 1056-1058). Surprisingly these R- and S-ibuprofen CoA thioesters prove to be potent and specific inhibitors of the activation of the nuclear transcription factor Nf-κB (figure 1). The reason for this surprising result was that these R- and S-CoA ibuprofen thioesters lead to an inhibition of the Nf-κB-dependent transcription (figure 2). Since the nuclear transcription factor Nf-κB is responsible for the formation of a series of proteins (cytokines) and enzymes (cyclooxygenase 2) with known proinflammatory properties (Barnes and Adcock, supra) the observed novel effect of the R- and S-thioesters appears to be of particular importance for the inhibition, reduction and limitation of the duration of all symptoms of acute and chronic inflammations. Thus for example it was shown that the induction of cyclooxygenase 2 which is mainly responsible for the formation of inflammatory prostaglandins (Seibert et al., Novel Molecular Approaches to Anti-inflammatory Theory, 1995, "Birkhäuser Verlag", Basel, AAS 46, p. 41) was blocked in inflammatory cells (monocytes of the blood) by the said thioesters since the said thioesters

not only inhibit the activation of Nf-κB but also the formation of the Nf-κB-dependent cyclooxygenase (figure 2).

A consequence of this invention is that the said thioesters of the R-enantiomer of ibuprofen are highly active inhibitors of the activation of Nf-κB by inflammatory stimuli and are hence specific, antiphlogistic and analgesic agents. They inhibit the formation of the Nf-κB-dependent inflammatory mediators especially in inflamed tissue.

The same applies to R-ibuprofen itself which is metabolized in the body to the said thioesters. In principle it is also possible within the scope of the invention to also use racemates of R-ibuprofen containing up to 49 % S-ibuprofen since in this case the effect of the R-ibuprofen would still dominate the undesired effects of S-ibuprofen which were described in the introduction. Derivatives of the said compounds which are metabolized in an analogous manner in the organism can also be used.

In addition there are also indications that the same mechanisms also occur with arylacetic acids or acetyl-salicylates. These compounds are therefore also encompassed by the invention.

The observation reported here contradicts the prior art which has previously not postulated an independent pharmacological (antiphlogistic or analgesic) effect for thioesters of ibuprofen or of the prodrug (A.M. Evans, Eur. J. Clin. Pharmacol. (1992) 42, p. 237-256; Klein, supra). This surprising finding led to the recognition

that precisely these thioesters, corresponding prodrugs and galenic products can be used advantageously for therapy because their use will be expected to reduce the undesired pharmacological effects while retaining the efficacy. (Cyclooxygenase 1 which is important for many organs is not inhibited (see above) but instead among others they block the formation of cyclooxygenase 2 which forms in the inflamed tissue as a result of the inflammation-dependent activation of Nf-κB). Thus in particular the ibuprofen thioesters are a novel and previously unknown active principle for inflammation. Their spectrum of action is presumably different (broader cf. e.g. A.S. Baldwin, Jr., Annu. Rev. Immunol. (1996) 14, 649-81) than that of known inhibitors of cyclooxygenases since various Nf-κB-dependent mediators are formed in a reduced amount. Their spectrum of side effects is presumably less since cyclooxygenase 1 is not inhibited.

In addition within the scope of the invention it appears to be possible to inhibit other Nf-κB-dependent processes which are in turn the basis of other diseases or unpleasant symptoms. These include for example the formation and growth of tumours, autoimmune diseases, allergic reactions etc. Hence in principle the pharmaceutical preparation according to the invention can also be used for the prophylaxis or treatment of all such manifestations which are based on Nf-κB-dependent processes.

Examples of active substances in the sense of this patent

1. R- and S-ibuprofen -(CoA)- thioesters and active (in

the same sense) derivatives thereof such as esters, salts and other common chemical compounds etc.

2. All prodrugs of ibuprofen thioesters such as e.g. R-ibuprofen and derivatives thereof provided they are metabolized in the organism to form CoA-thioesters.

3. All pharmacological preparations that are active in the same sense e.g. racemic mixtures of R-ibuprofen containing up to 49 % S-ibuprofen.

As already described in the text, figures 1 and 2 show the basis of the present invention:

Figure 1

Influence of R-ibuprofen CoA-thioesters on the activation of the transcription factor Nf-κB in Jurkat cells. The electro mobility shift assay (DIG Gel Shift Kit, Boehringer Mannheim) shows that a two hour pre-incubation with different concentrations of R-ibuprofen thioester (100, 10 and 1 ptm) causes an activation inhibition of Nf-κB (lanes 3-5) in phorbol ester (TPA) stimulated Jurkat cells. Lane 1 shows the unstimulated cells and lane 2 shows the stimulated control cells.

Fig 2: Inhibition of PGHS-2 by R-ibuprofenoyl-CoA

Lane 1: 1.0 mM ibuprofen, racemic
Lane 2: 0.1 mM ibuprofen, racemic
Lane 3: 0.05 mM ibuprofen, racemic
Lane 4: 0.5 mM R-ibuprofenoyl-CoA
Lane 5: 0.25 mM R-ibuprofenoyl-CoA

Lane 6: 0.05 mM R-ibuprofenoyl-CoA
Lane 7: control, medium + LPS

Incubation of LPS-induced monocytes (24 hours). The figure shows that in contrast to racemic ibuprofen (R- and S-ibuprofen), R-ibuprofenoyl-CoA thioester leads to a dose-dependent suppression of the formation of PGHS-2 (cyclooxygenase-2).
Method according to: BRIDEAU, C., KARGMAN, S., LIU, S., DALLOB, A.L., EHRICH, E.W., RODGER, I.W. & CHAN, C.C. (1996). A human whole blood assay for clinical evaluation of biochemical efficacy of cyclooxygenase inhibitors, Inflamm. Res., 45, 68-74.

PCT/EP98/02318

Claims

1. Pharmaceutical preparation containing CoA-thioesters of arylpropionic acids, arylacetic acids or acetylsalicylates or R- or/and S-ibuprofen-CoA-thioesters.

2. Use of a pharmaceutical preparation as claimed in claim 1 for the indications of acute or/and chronic pain, inflammations of any genesis and to treat all other symptoms of inflammatory processes.

3. Use of CoA-thioestersof arylpropionic acids, arylacetic acids or acetylsalicylates or R- or/and S-ibuprofen thioesters to produce a pharmaceutical preparation for the indications of acute or/and chronic pain, inflammations of any genesis and to treat all other symptoms of inflammatory processes.

4. Use of pharmaceutical preparations as claimed in claim 1 or of R-ibuprofen or racemates of ibuprofen containing up to 49 % S-ibuprofen or derivatives of the said compounds that are metabolized in an analogous manner in the organism to inhibit Nf-κB-dependent processes in the formation or growth of tumours, in autoimmune diseases or allergic reactions.

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5. Use of CoA-thioesters of arylpropionic acids, arylacetic acids or acetylsalicylates, R-ibuprofen or racemates of ibuprofen containing up to 49 % S-ibuprofen or derivatives of the said compounds containing up to 49 % S-ibuprofen to produce a pharmaceutical preparation for the inhibition of Nf-κB-dependent processes in the formation or growth of tumours, in autoimmune diseases or allergic reactions.

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Fig. 1

Inhibition of Nf-κB activation by R-ibuprofen-CoA-thioester

TPA	-	+	+	+	+
R-Ibuprofen-CoA-Thioester [μM]	-	-	100	10	1

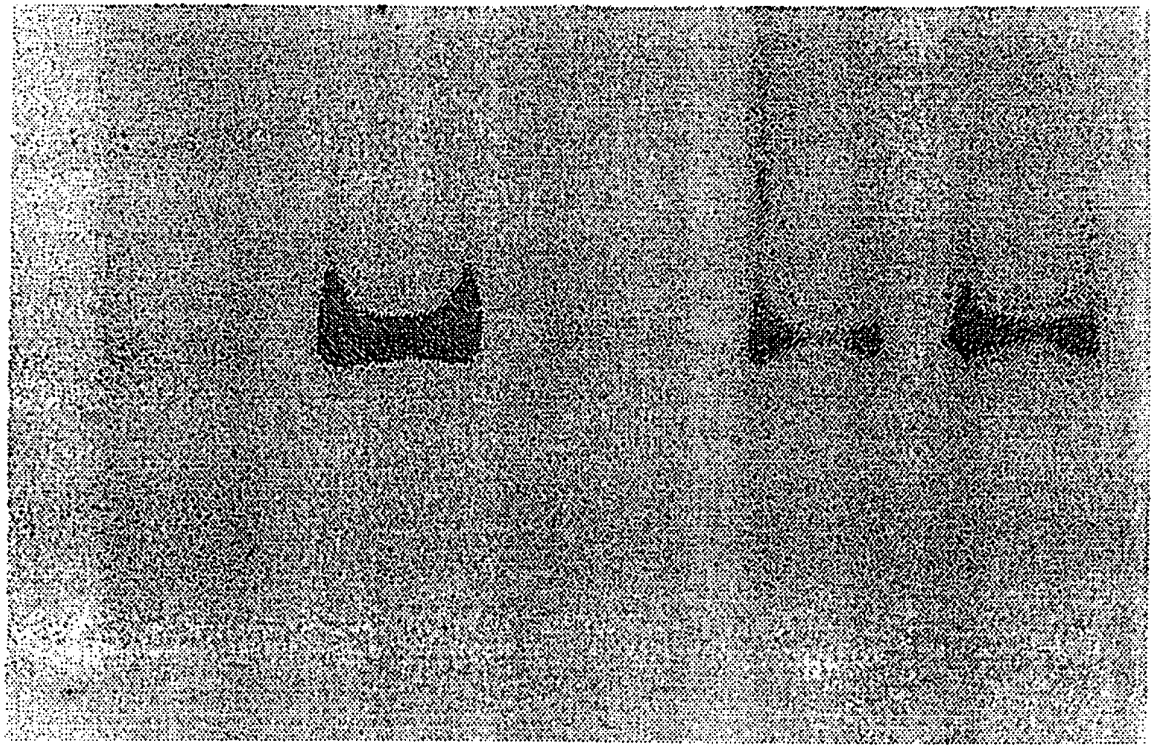

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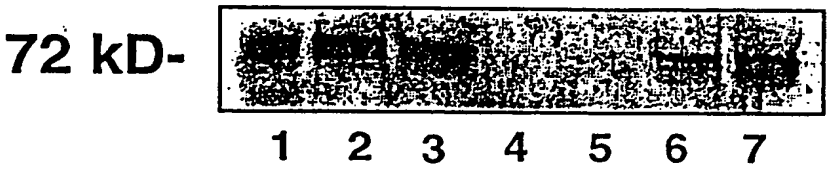
Fig. 2



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October 3, 2005

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Application No.	:	**2,362,888**
Owner	:	PAZ ARZNEIMITTEL-ENTWICKLUNGSGESELLSCHAFT MBH
Title	:	**USE OF R-ARYL PROPIONIC ACIDS FOR PRODUCING MEDICAMENTS TO TREAT DISEASES IN HUMANS AND ANIMALS, WHEREBY SAID DISEASES CAN BE THERAPEUTICALLY INFLUENCED BY INHIBITING THE ACTIVATION OF NF-KB**
Classification	:	A61K-31/192
Your File No.	:	**11950-4-N.P.**
Examiner	:	Tania Nish

YOU ARE HEREBY NOTIFIED OF A REQUISITION BY THE EXAMINER IN ACCORDANCE WITH SUBSECTION 30(2) OF THE *PATENT RULES*. IN ORDER TO AVOID ABANDONMENT UNDER PARAGRAPH 73(1)(A) OF THE *PATENT ACT*, A WRITTEN REPLY MUST BE RECEIVED WITHIN 6 MONTHS AFTER THE ABOVE DATE.

This application has been examined taking into account the:

Description,	pages 1-15, as received on August 13, 2001 during the national phase;
Claims,	1-7, as received on August 13, 2001 during the national phase; and
Drawings,	pages 1-6, as received on August 13, 2001 during the national phase.

The number of claims in this application is 7.

The examiner has identified the following defects in the application:

The search of the prior art has revealed the following:

References Applied:

United States Patents			
5,200,198	April 6, 1993	Geisslinger et al.	D1
5,331,000	July 19, 1994	Young et al.	D2
PCT Application			
WO 98/09603	March 12, 1998	Wechter et al.	D3

Canadian Application			
2,287,501	October 29, 1998	Bang et al.	D4

D1 discloses medicaments comprising R-flurbiprofen for the treatment of pain and inflammatory diseases.

D2 discloses the use of R-ketoprofen as an antipyretic and analgesic in the treatment of pain associated with rheumatoid arthritis, inflammation, graft rejection, malignancy and other disease states.

D3 discloses composition comprising 2-arylpropionic acid R-NSAIDS for therapeutic and prophylactic treatment of inflamation, neoplasia, cystic fibrosis and Alzheimer's disease.

D4 disclose thioesters of R-arylpropionoc acids and pro-drugs thereof for use in the treatment of the symptoms of the inflammatory processes.

Claims 1-7 do not comply with paragraph 28.2(1)(*a*) of the *Patent Act*. The subject-matter defined by these claims was disclosed by D4 more than one year before the filing date of the present patent application. D4 discloses pharmaceutical preparation of R-arylpropionoc acids or pro-drugs thereof inhibit NF-κB dependent processes which is the basis of inflammatory diseases, auto-immune disease, neoplasia and allergic reactions. Therefore, the claims lack novelty.

Claims 1-7 do not comply with paragraph 28.2(1)(*b*) of the *Patent Act*. D1 to D3 disclosed the claimed subject matter before the claim date. D1 discloses medicaments comprising R-flurbiprofen or salts thereof for the treatment of pain and inflammatory diseases. The composition contains about 60-99.5% of the R-isomer. The medicaments are disclosed for enteral or parenteral administration of tablets, dragees, powders, granulates, suppositories or solutions. The effective dose is disclosed as 10-100 mg. Therefore, claims 1-7 are anticipated by D1.

D2 discloses the use of a medicament comprising R-ketoprofen or a pharmaceutically acceptable salt thereof as an antipyretic and analgesic in the treatment of pain associated with rheumatoid arthritis, inflammation, graft rejection, malignancy and other disease states. The compound is disclosed as being "substantially free of its S-isomer" contains at least 99% by weight of R-ketoprofen. D2 disclosed the dosage as a range of 25-200 mg in the form of tablets, troches, dispersions, suspensions, solutions, capsules and patches for enteral or parenteral administration. Therefore, claims 1-7 lack novelty with respect to D2.

D3 discloses compositions comprising 2-arylpropionic acid R-NSAIDS or pharmaceutically acceptable salts thereof for therapeutic and prophylactic treatment of inflamation, neoplasia, cystic fibrosis and Alzheimer's disease. D3 discloses that the composition comprises of at least 99% by weight or the R-NSAIDs, such as those defined in claim 1 of the current application. The dosage range is disclosed as 01. mg to 2000 mg for oral solid, suspension, solutions or emulsion forms. Therefore, D3 anticipates claims 1-7.

Claim 1 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. brackets are not allowed in the claims. Therefore, all parentheses must be removed.

Furthermore, claim 1 is indefinite as the inclusion of "and/or" causes ambiguity.

Claims 2, 4 and 7 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The following terms have no antecedents:

"the agent" (claim 2)
"the active material" (claim 4)
"the active materials" (claim 7)

Claim 4 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. The inclusion of "preferably" causes ambiguity. This expression raises uncertainty so as to the presence of the specific statement to which it relates.

Claim 5 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. The inclusion of "usual adjuvent and carrier materials" causes ambiguity. The description describes "pharmaceutically compatible carrier material" on page 17. For clarity in construing the claims, the terms of the claims should be coterminous with the terms of the description.

Claim 6 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. The inclusion of "other orally usable forms" causes ambiguity. Furthermore, "dragees" are not described in the description.

Claim 7 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. The subject matter of the claim is unclear.

In view of the foregoing defects, the applicant is requisitioned, under subsection 30(2) of the *Patent Rules*, to amend the application in order to comply with the *Patent Act* and the *Patent Rules* or to provide arguments as to why the application does comply.

Under section 34 of the *Patent Rules*, any amendment made in response to this requisition must be accompanied by a statement explaining the nature thereof, and how it corrects each of the above identified defects.

Tania Nish
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819-934-3592